UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,795	09/05/2001	Gunther Berndl	49727	4232

26474 7590 04/16/2007

NOVAK DRUCE DELUCA & QUIGG, LLP
1300 EYE STREET NW
SUITE 1000 WEST TOWER
WASHINGTON, DC 20005

EXAMINER	
LANDAU, SHARMILA GOLLAMUDI	
ART UNIT	PAPER NUMBER
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/914,795	BERNDL ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-10 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request fro Continued Examination and Amendments/Remarks filed 3/14/07 is acknowledged. Claims **2-10 and 19** are pending in this application. Claims 1 and 11-18 stand cancelled.

Withdrawn Rejections

The rejection of claims 2-10 and 12-18 is withdrawn under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicant's amendments and cancellation of claims in the response of 3/14/07.

The rejection of claims 2, 5-8, 11-14, and 17-18 under 35 U.S.C. 102(b) as being anticipated by EP 0564945 is withdrawn in view of applicant's amendments and cancellation of claims in the response of 3/14/07.

The rejection of claims 5-7, 11-12, 14, 16-18 under 35 U.S.C. 102(e) as being anticipated by Stella et al (6,046,177) is withdrawn in view of applicant's amendments and cancellation of claims in the response of 3/14/07.

The rejection of claims 11, 14-15, and 17 under 35 U.S.C. 102(e) as being anticipated by Baert et al (6,365,188) is withdrawn in view of applicant's amendments and cancellation of claims in the response of 3/14/07.

The rejection of claims 2, 8-10, 13 under 35 U.S.C. 103(a) as being unpatentable over Stella et al (6,046,177) is withdrawn in view of applicant's amendments and cancellation of claims in the response of 3/14/07.

The rejection of claims 3-4 under 35 U.S.C. 103(a) as being unpatentable over Stella et al (6,046,177) in view Klimesch et al (4880585) is withdrawn in view of applicant's amendments and cancellation of claims in the response of 3/14/07.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2-10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baert et al (6,365,188) in view of Stella et al (6,046,177) in further view of Oshlack et al (6306438) or Murata et al (5,500,221) respectively.

Baert et al teach a solid mixture of cyclodextrin prepared via melt extrusion. The melt-extrusion mixture contains cyclodextrin and an active agent. See column 3, lines 26-40. Baert discloses that cyclodextrins increase the solubility of the insoluble drugs such as anti-fungals, specifically itraconazole. Any suitable compound may be utilized provided that the drug does not decompose at high temperatures. See column 2, lines 45-60. Baert teaches the use of substituted

and unsubstituted cyclodextrins including beat-cyclodextrin, hydroxypropyl-β-cyclodextrin, and sulfobutylcyclodextrins. See column 7 in its entirety and specifically lines 61 and column 8, lines 4-10. Baert teaches melt-extrusion as the polymer extrusion technique wherein an active agent is embedded in one or more carriers. In this technique the active and excipients are molten in the extruder and hence embedded in the thermoplastic and thermomelting polymers. See column 3, lines 26-40. Additionally, the mixture may contain additives such as instant polyethylene glycol. See column 4, lines 34-42. The process includes a) mixing the cyclodextrin with the active agent and additives, b) mixing optional additives, c) heating the mixture until melting of one of the components occurs, d) forcing the mixture through one or more nozzles, and e) cooling the mixture to obtain a solid product. See column 4, lines 15-25. Although, a temperature of 239 degrees Celsius is exemplified, Baert discloses that different temperatures may be applied and discloses the method of ascertaining the required temperature. See column 5, lines 1-12. The extruder has counterotating screw with different shapes. See column 5. The melt-extruded mixture is preferably prepared without water or a solvent. The preferred ratio of the active to cyclodextrin is 1:3. See column 7, lines 64 to column 8, lines 4 and examples.

Baert et al do not specify the optional additives or the weight percent of the optional additives. Additionally, Baert does not teach the instant temperature of 170 degrees Celsius.

Stella et al teaches controlled release forms of solid formulations containing sulfoalkyl ether cyclodextrin (SAE-CD). The controlled release formulation contains a core containing an active agent, at least on SAE-CD, at least one rate controlling modifier, and at least one pharmaceutical acceptable excipient. See column 6, lines 1-7. The core may be made by several methods including melt extrusion. Note example 10. The release rate modifier provides either a

delayed, sustained, timed, or targeted release of the active agent. See column 27, lines 40-50. Stella teaches varying the ratio of the rate controlling modifier and the drug such as 10:1 and 5:1, determines the release rate. The rate control modifier (exemplified HPMC) is varied from 25% to 50%. See column 17. Stella et al teach a controlled release device comprising 5% of prednisone; 35% SAE-β-CD; 50% HPMC (modified natural polymeric binder as defined by page 4 of the specification); and 10% lactose (excipient). See column 18, lines 27-35. Other release rate modifiers include HPMC, HPC, cellulose acetate butyrate, cellulose acetate propionate, cellulose propionate, carrageenan, cellulose acetate, cellulose nitrate, methylcellulose, hydroxyethyl cellulose, ethylcellulose, polyvinyl acetate, latex dispersions, acacia, tragacanth, guar gum, and gelatin. See column 39, lines 10-20.

Further, Stella teaches the use of binders such as celluloses, polyethylene glycols, polyvinylpyrrolidone, vinyl alcohol polymers, in order to obtain suitable products. See column 27, lines 5-30. Some of the binders named also function as the release rate modifier. See column 27, lines 48-50. The binder is utilized in different proportions in different examples. The example on column 37 utilizes 43% of EMDEX (a binder). Example 10 discloses a process utilizing melt extrusion wherein 2.5% of an active, 67.5% of SAE-CD, 10.5% PEG 6000, and excipients are melted at 60 degrees Celsius to form granules.

Oshlack teaches a stabilized sustained release tramadol formulation made by melt extrusion using counter-rotating screws. See abstract and example 1. Oshlack teaches the release of the active agent from the controlled release formulation is influenced or adjusted to a desired rate, by the addition of one or more release-modifying agents into the matrix. The release-modifying agent comprises one or more water-soluble hydrophilic polymers in order to modify

the release characteristics of the formulation. Examples of suitable polymers include hydroxypropylmethylcellulose, cellulose ethers, acrylic resins and protein-derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, etc. see column 10, line 60 to column 11, line 10.

Murata et al teach a sustained release suppository. Murata teaches the polymers that are utilized for adjusting the release rate of drugs are water-soluble polymers such as hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone, methylcellulose, etc. see column 3, lines 20-36.

It would have been obvious at the time the invention was made to combine the teachings of Baert et al and Stella et al and utilize the a polymer as the additive in Baert's process. Firstly, one would have been motivated to do so since Stella teaches the use of a rate controlling modifiers, such as exemplified HPMC, control the release rate of the active to provide for a delayed, targeted, sustained, etc. dosage form. Therefore, one would have been motivated to add a polymer such as instant polymer in the instant amount, to modify the release rate of the dosage form. Further, it would have been obvious to utilize the polymer in the instant weight percent since Stella teaches the concentration of the rate controlling polymer determines the release rate. Therefore, depending on the release rate of the active, a skilled artisan would have been motivated to adjust the concentration accordingly. For instance, if one desired a slow release rate, a skilled artisan would have been motivated to add 50% of the polymer.

Secondly, one would have been further motivated to look to Oshlack and utilize instant PVP since Oshlack teaches the functional equivalency of Stella's exemplified rate-releasing

modifier HPMC and instant PVP. Therefore, one would have been motivated to utilize the instant PVP with the expectation of similar results since the prior art teaches the functional equivalency of Stella's HPMC and PVP as polymers that adjust the release rate of drugs in a dosage form. Furthermore, Stella also states that the binders taught, among which PVP is taught, may also function as the rate controlling modifier; thus one would expect the instant PVP to act as a rate controlling modifier in Baert's dosage form.

Alternatively, it would have been obvious for a skilled artisan to look to Murata and utilize instant PVP since Murata teaches the functional equivalency of Baert et al's exemplified rate-releasing modifier HPMC and instant PVP. Therefore, one would have been motivated to utilize the instant PVP with the expectation of similar results since the prior art teaches the functional equivalency of Stella's HPMC and PVP as polymers that adjust the release rate of drugs in a dosage form. Furthermore, Stella also states that the binders taught, among which PVP is taught, may also function as the rate controlling modifier; thus one would expect the instant PVP to act as a rate controlling modifier in Baert's dosage form.

With regard to the temperatures, the examiner points out that Baert teaches the use of various cyclodextrin derivates including sulfobutyl cyclodextrins, thus the melt extrusion temperature depends on the type of the cyclodextrin used and the components in the composition itself. Therefore, if one utilized a composition comprising the polymer additive and a sulfoalkyl ether cyclodextrin, one would have used a temperature such as 60 degrees Celsius as taught by Stella et al. Further, a skilled artisan would have reasonably expected success in the variation of the temperature since Baert teaches that different temperatures may be applied and discloses the method of ascertaining the required temperature.

With regard to claims 9 and 10, absent the unexpectedness of mixing the polymer and cyclodextrin prior to mixing the drug, it is the examiner's position that the sequence in which the components are mixed and melted would not effect the process since all the components are rendered in a "plasticized", i.e. melted state.

Response to Arguments

Applicant argues that the examiner has used impermissible hindsight since Baert teaches away from using additives during the method of melt extruding the cyclodextrin and active.

Applicant's arguments filed 3/14/07 have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In instant case, Baert teaches the use of any suitable additive during the process of melt extrusion process. Although Baert does not teach the instant additive, it is clear that any pharmaceutically acceptable additive may be used. Thus, the inclusion of an additive in the melt extrusion composition is not hindsight reasoning since this is clearly taught by Baert and Baert does not teach away from the adding additives such as rate controlling excipients in the melt extrusion process as argued by applicant. The secondary reference, Stella, teaches the use of release rate modifying polymers in a composition comprising cyclodextrin and an active agent. The purpose of the polymer is to manipulate the release rate wherein a higher

concentration (50%) slows the release rate and a lower concentration provides faster release. Further, Stella teaches the dosage form may be made by melt extrusion wherein a temperature of 60 degrees Celsius is used. Thus, the melt extrusion temperature would vary according to the components in the composition. Although Baert exemplifies a temperature of 239 degrees Celsius, Baert discloses that different temperatures may be applied depending on the composition and discloses the method of ascertaining the required temperature. Clearly, the temperature exemplified by Baert is not critical since as taught by Baert, it depends on the components in the composition. Thus, the manipulation of the temperature is not hindsight reasoning since the reference itself teaches the manipulation of the temperature as discussed above. Moreover, applicant argues that the temperature taught by Baert must melt either the cyclodextrin or the active agent. The examiner points out that the preferred drug, itraconazole, has a melting temperature of 166.2 degrees Celsius and as argued by applicant, Baert teaches a temperature must melt either the cyclodextrin or the active agent. Thus, clearly a temperature of less than 170 degrees Celsius would be suitable. Furthermore, the examiner points out that Baert teaches the use of various cyclodextrins including sulfoalkyl cyclodextrins. The examiner points out that depending on the type of cyclodextrin used, the melt extrusion temperature would also change. Thus, if one used a sulfoalkyl-cyclodextrin, then one would use the melt extrusion temperature taught by Stella et al, which is 60 degrees Celsius.

With regard to the claimed weight percents, the examiner points out that

Therefore it is the examiner's position that the instant claims are prima facie obvious for the reasons discussed above.

Claims 2-10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuboi et al (6,063,393) by itself or in view of Klimesch et al (4,880,585).

Tsuboi teaches a method of controlling insects. The solid composition comprises a fungicide or insecticide and a substance that forms a matrix and functions as the solid carrier. This substance is preferably a polymeric carrier materials. Tsuboi teaches the preference for polymers that can be processed as thermoplastics and have a processing time of 50-260 C. Tsuboi teaches various polymeric materials including vinyl polymers (see column 17, line 36), high molecular weight polyethylene glycols (PEG) (see examples 11 and 13). Example 3 discloses a process wherein 20 parts cyfluthrin, 0.1 parts triadminenol, 80 parts beta-cyclodextrin, 150 parts of a polymeric material Biopol polymeric carries), and 50 parts Carbowax 20M (polyethylene glycol polymeric carrier), are homogenized in an extruder at a temperature of 160°Celsius and then injection molded to a shaped form. The polymeric carrier is utilized in various weight percents including 50% and above. Note examples and example 3. With regard to claim 6, it is noted that the active and cyclodextrin implicitly form a complex during the process of melting the components and the reference does not explicitly state that the active and cyclodextrin are maintained in an uncomplexed state. Tsuboi teaches the type of shaping can be produced by any known method in the art. see column 23, lines 20-25.

Although Tsuboi suggests the use of vinyl polymers and uses high molecular weight polyethylene glycols (3000-7000MW and 7800-9000), one cannot immediately envisage the use of polyethylene glycols in example 3 specifically. Further, although Tsuboi suggests the use of vinyl alcohols, Tsuboi does not specify the use of polyvinylpyrolidone.

Klimesch et al teaches a method of continuous tableting using a molding calendar with opposite rollers (col. 1, lines 16-27). Klimesch teaches extrudable mixtures are mixtures of one or more active compounds with one or more auxiliaries, which are conventionally used in the preparation of pharmaceutical tablets and are pasty and therefore extrudable due to the melting or softening of one or more components. These include polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone (NVP) and vinyl acetate, copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, polyvinyl alcohol, ethylene/vinyl acetate copolymers, polyhydroxyethyl methacrylate, copolymers of methyl methacrylate and acrylic acid, cellulose esters, cellulose ethers, polyethylene glycol and polyethylene. Klimesch teaches the polymeric binder must soften or melt at from 50 to 180 degrees C. preferably from 60 to 130 degrees C. and the NVP polymers have a melt temperature below 120 degree C. see column 3, lines 1-65. Klimesch teaches the process provides a simple, continuous method of tableting wherein the mixture is extruded and the still deformable extrudate is pressed between two rollers which are driven in opposite directions and possess depressions opposite one another in the roller shell (molding calendar), the form of these depressions determining the tablet shape. Thus, the process eliminates premixing (col. 1, lines 16-27 and 28-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Tsuboi and Klimesch and substitute the polymeric carrier taught in Tsuboi's example 3 and utilize the instantly claimed polymers. One would have been motivated to do so with a reasonable expectation of success since Tsuboi suggests the use of various polymers including vinyl polymers and teaches the use of high molecular weight PEG polymers. Therefore, absent the unexpectedness of the instant polymers, it would have been

obvious to substitute one polymeric carrier for another with the expectation of success. Furthermore, it would have been obvious to look to Klimesch and expect similar results in using polyvinylpyrolidone (a vinyl polymer) or polyethylene glycol as the polymeric carrier since Klimesch teaches these polymers are known thermoplastic polymers used in melt extrusion processes. It is noted that Tsuboi is directed to a plant treatment compositions and Klimesch is directed to pharmaceutical compositions; however the examiner points out that " it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention." In instant case, Klimesch is reasonably pertinent to the particular problem, i.e. the use of polymeric carriers in melt extrusion processes.

Regarding claims 3-4, it would have been obvious to a skilled artisan to utilize a molding calendar in the extrusion process since Tsuboi teaches the use of any known method to shape the product and Klimesch et al teach using mold calendaring to produce certain shapes.

Regarding claim 7, it is the examiner's position that EP would have similar, if not the same, functional properties since the prior art composition is substantially similar. See MPEP2112 IV, V and 2112.01.

Regarding claims 9 and 10, absent the unexpectedness of mixing the polymer and cyclodextrin prior to mixing the drug, it is the examiner's position that the sequence in which the components are mixed and melted would not effect the process since all the components are rendered in a "plasticized", i.e. melted state.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharmila S. Gollamudi
Primary Examiner
Art Unit 1616

SSG